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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/331,980	11/26/1999	JEAN-LUC CHAGNAUD	19141-006	2351

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IVOR R ELRIFI
MINTZ LEVIN COHN FERRIS
GLOVSKY & POPEO
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/331,980	Applicant(s) CHAGNAUD ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/4/02; 11/19/01* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5, and 7-14* is/are pending in the application.

4a) Of the above claim(s) *7-10 and 12-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 11 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-5 and 7-14 are pending.

2. Claims 7-10, 12-13 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 3/4/02 and 2/5/02, the following objections and rejection remain.

4. The request for amending the specification has not been entered in view of the substitute specification filed 3/4/02 because the specify entries on page 2-8 of the amendment filed on 3/4/02 can no longer be found in the substitute specification. Further, the disclosure is objected to because of the following informality: (1) the mail box symbols and radioisotope symbol on page 12 line 15 should have been an arrow "→"; (2) a period "." is missing at the end of a sentence on page 5, line 24; (3) all semi-comma on page 3-5 should be a period at the end of the sentence; (4) "N02" on page 20 line 6 should have been "NO2"; (5) "anti-IFNg" on page 20 line 19 should have been "anti-IFNγ"; (6) "IFN-g" on page 24, line 11 should have been "IFNγ"; (7) "TFN-a/b" on page 24, line 11 should have been "TNF-α/β"; (8) "beforex" on page 26, line 5 requires a space between "before" and "x"; (9) "}" on page 26, line 23 should have been ")"; (10) the article "le" on page 28 line 30 should have been "the"; (11) the conjunction "et" on page 28 line 14 and page 53 line 5 should have been "and"; (12) "4x 10-9M" on page 45 line 8 and page 46 line 10 should have been "4x 10^{-9} M"; (13) SEQ ID NO is required on page 56 line 1. Appropriated correction is required.

5. The abstract of the disclosure is objected to because it is not a single paragraph. Correction is required. See MPEP § 608.01(b).

6. The drawings, filed 3/4/02, are not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Boullerne *et al.* (of record, J. of Neuroimmunology 60: 117-124, 1995; PTO 892) for the same reasons set forth in Paper No 10.

Applicants' arguments filed 3/4/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) Boullerne *et al* does not anticipate amended claims 1-4 which claim 1 now recites a purified antibody wherein the antibody binds specifically to a nitrosylated protein; (2) Boullerne *et al* concerns the nitrosation of amino acid conjugates and the use of NO amino acid-g-BSA conjugates to coat a plate for ELISA, (3) Boullerne *et al* does not provide any teaching directed to the use of a purified antibody, (4) Boullerne *et al* teach that the antibodies in the sera of patient with multiple sclerosis simply recognize nitrosylated protein and (5) claims 2-4 depend directly from amended claim 1 and thus incorporate all the limitations of claim 1.

However, the amended claim 1 still reads on the reference antibody. A product is a product irrespective of how it is made. Further, the reference antibody binds specifically to a nitrosylated protein such as nitrosylated bovine serum albumin. In response to applicant's argument that the reference fails to provide any teaching directed to the use of a purified antibody, it is noted that the feature upon which applicant relies (i.e., the use of a purified antibody) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, a product is a product irrespective of how it is use.

Boullerne *et al* teach a purified antibody that binds specifically to a nitrosylated protein such as nitrosylated bovine serum albumin and a method of making the immunogen which composed of a nitrosylated carrier protein (nitrosylated bovine serum albumin) or a nitrosylated amino acid (cysteine) coupled to a carrier (bovine serum albumin) by a coupling agent which is glutaraldehyde (g) (See NO-Cys-g-BSA in **Materials and Methods**, pp. 118-119, in particular).

The reference antibody to the nitrosylated bovine serum albumin can be use in Enzyme-linked immunosorbent Assay (ELISA) to detect nitrosylated protein in the sera of patients with multiple sclerosis (See page 119, column 1, in particular). Boullerne *et al* further teach that NO production may be involved in autoimmune diseases such as IDDM, SLE, autoimmune neuropathy of Chagas' disease caused by trypanosoma cruzi and the use of conjugated haptens (nitrosylated cysteine cross-linked to BSA) is very helpful in defining the specific antibody responses (See page 123, column 1, last paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

9. The following new grounds of rejections are necessitated by the amendment filed 3/4/02 and 2/5/02.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-3, 5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boullerne *et al.* (of record, J. of Neuroimmunology 60: 117-124, 1995; PTO 892) or Stamler *et al*, (of record, Proc. Natl. Acad. Sci USA 89: 444-448, 1992; PTO 892) each in view of U.S. Pat No. 6,090,382 (July 2000, PTO 892) and Campbell *et al* (of record, Monoclonal antibody technology , Elsevier Science Publishers, 1984) or Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149).

Applicants' arguments filed 3/4/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) it cannot be said that one skilled in the art would deem it obvious from a combination of these two references to produce purified antibodies which recognize and specifically bind to a nitrosylated protein as recited in claim 1. One skilled in the art is faced with several obstacles to obtain such purified antibodies capable of recognizing in vivo S-nitrosoproteins and which neutralize their properties; (2) claim 11 has been amended to recite a pharmaceutical composition comprising (a) a purified antibody that binds specifically to a nitrosylated protein and (b) a pharmaceutically acceptable vehicle.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., purified antibodies capable of recognizing **in vivo** S-nitrosoproteins and which **neutralize** their properties) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Boullerne *et al* teach nitrosylated carrier protein such as nitrosylated bovine serum albumin or a nitrosylated amino acid (cysteine) coupled to a carrier (bovine serum albumin) by a coupling agent which is glutaraldehyde (g) (See NO-Cys-g-BSA (See Materials and Methods, pp. 118-119, in particular). Boullerne *et al* teach antibody to the nitrosylated bovine serum albumin can be use in Enzyme-linked immunosorbent Assay (ELISA) to detect nitrosylated protein in the sera of patients with multiple sclerosis (See page 119, column 1, in particular). Boullerne *et al* further teach that NO production may be involved in autoimmune diseases such as IDDM, SLE, autoimmune neuropathy of Chagas' disease caused by trypanosoma cruzi and the use of conjugated haptens (nitrosylated cysteine cross-linked to BSA) is very helpful in defining the specific antibody responses (See page 123, column 1, last paragraph, in particular).

Stamler *et al* teach a method of synthesizing S-Nitroso proteins such as nitroso BSA, t-PA, Cathepsin B and human plasma. Stamler *et al* further teach nitric oxide (NO) has a half-life in the order of 0.1 second *in vivo* and nitrosylation of NO increases the half-life of these NO molecules to about 24 hour (See page 444, column 1, 1st paragraph; page 445, column 2 Results; page 446, column 1, last paragraph, in particular).

The claimed invention as recited in claim 5 differs from the reference only by the recitation of that the antibody is a monoclonal antibody.

The claimed invention as recited in claim 11 differs from the reference only by the recitation of a pharmaceutical composition comprising (a) a purified antibody that binds specifically to a nitrosylated protein and (b) a pharmaceutically acceptable vehicle.

Campbell *et al* teach that "[i] it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (See page 29, section "Basic research", in particular).

Harlow *et al* teach a method of producing monoclonal antibody (See page 139-149, in particular). Harlow *et al* further teach that the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular).

The '382 patent teaches a pharmaceutical composition comprising an antibody that binds to human TNFα and a pharmaceutical acceptable carrier or excipient such as sterile saline (See column 20 lines 57, bridging column 21, line 1-52, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody as taught by Campbell *et al* or Harlow *et al* with the nitrosylated protein as taught by Boullerne *et al* or Stamler *et al* for a pharmaceutical composition comprising a monoclonal antibody that binds specifically to the nitrosylated protein and a pharmaceutical excipient as taught by the '382 patent, Campbell *et al*, Harlow *et al* and Boullerne *et al* or Stamler *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody fragment because Harlow *et al* teach the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page

141, last full paragraph, in particular). Campbell *et al* teach that "[i] it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (See page 29, section "Basic research", in particular). Boullerne *et al* teach antibody to the nitrosylated bovine serum albumin can be use in Enzyme-linked immunosorbent Assay (ELISA) to detect nitrosylated protein in the sera of patients with multiple sclerosis (See page 119, column 1, in particular); NO production may be involved in autoimmune diseases including IDDM, SLE, autoimmune neuropathy of Chagas' disease caused by trypanosoma cruzi and the use of conjugated haptens (nitrosylated cysteine cross-linked to BSA) is very helpful in defining the specific antibody responses (See page 123, column 1, last paragraph, in particular). Stamler *et al* teach nitric oxide (NO) has a half-life in the order of 0.1 second *in vivo* and nitrosylation of NO increases the half-life of these NO molecules to about 24 hour (See page 444, column 1, 1st paragraph; page 445, column 2 Results; page 446, column 1, last paragraph, in particular).

13. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boullerne *et al.* (of record, J. of Neuroimmunology 60: 117-124, 1995; PTO 892) or Stamler *et al*, (of record, Proc. Natl. Acad. Sci USA 89: 444-448, 1992; PTO 892) each in view of U.S. Pat No. 5,919,543 (July 1999, PTO 892) and Campbell *et al* (of record, Monoclonal antibody technology , Elsevier Science Publishers, 1984) or Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149) as applied to claims 1-3, 5 and 11 above, and further in view of U.S. Pat No. 5,858,682 (of record, Jan 1999, PTO 892; see entire document) for the same reasons set forth in Paper No 10.

Applicants' arguments filed 3/4/02 have been fully considered but are not found persuasive.

Applicants' position is that amended claim 14 now recites a kit for in vitro detection of nitrosylated proteins in a biological specimen comprising (a) purified antibody that binds specifically to a nitrosylated protein and (b) reagents to produce a medium favorable for an immunological reaction between said purified antibody and any nitrosylated proteins that may be present in a biological specimen.

However, the active ingredient in the kit is still the same antibody as the reference antibody which binds to nitrosylated protein as taught by Boullerne *et al,* Stamler *et al,* Campbell *et al, and* Harlow *et al*. Further, Boullerne *et al* teach antibody to the nitrosylated protein such as

bovine serum albumin can be use in Enzyme-linked immunosorbent Assay (ELISA), which is in vitro detection of nitrosylated protein in biological specimen such as sera of patients with multiple sclerosis (See page 119, column 1, in particular).

The combined teachings of the references have been discussed supra.

The claimed invention in claim 14 differs from the references only by the recitation of a kit comprising antibody for detection of any nitrosylated proteins in a biological specimen.

The '682 patent teaches a kit comprising antibody for diagnostic (See column 3, line 40; column 6, line 17; column 8, line 36, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody in a kit taught by '682 with the antibody that binds nitrosylated protein taught by as taught by Boullerne *et al,* Stamler *et al,* Campbell *et al, and* Harlow *et al* for the detection of nitrosylated protein immune complex in any biological specimen as taught by Boullerne *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One would have been motivated, with a reasonable expectation of success, to place the antibody in a kit for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '682 (See column 8, line 36-57, in particular).

14. INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85
New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. **Corrections other than Informalities Noted by Draftsperson on form PTO-948.**
All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before

the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

3. Timing of Corrections
Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
May 20, 2002

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640